Beta brachytherapy of an old degenerated saphenous vein graft with occlusive in-stent restenosis

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We report a case of obstructive in-stent restenosis in a diffusely diseased saphenous vein graft complicated by a non-ST-elevation myocardial infarction.

With tirofiban infusion, the extensively occluded saphenous bypass was reperfused, establishing a TIMI flow 3, and then entirely irradiated with a beta source (^{32}P) without any complication. At 7 months the patient was asymptomatic and the control angiogram did not reveal any restenosis.

In conclusion, ^{32}P beta brachytherapy may be extremely effective not only in case of native vessel in-stent restenosis but also in cases of high-risk vein graft in-stent restenosis.

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Introduction

Saphenous vein graft (SVG) disease after coronary artery bypass surgery is associated with a 15-30% graft failure rate at 1 year and with a 50% occlusion rate at 10 years[1]. Aggressive LDL-lowering therapy (levels < 100 mg/dl) but not low-dose warfarin has been found to be efficacious in delaying the progression of atherosclerosis of SVG[2].

Redo coronary artery bypass graft (CABG) is associated with increased rates of perioperative morbidity (3-11%) and mortality (3-7%)[3]. Repeat coronary surgery is also less effective for symptom relief with respect to the initial operation[4]. The percutaneous treatment of SVG is associated with high rates of procedural complications and restenosis, particularly in case of old and diffusely degenerated grafts. Angiographic restenosis at 6 months has been reported in up to 45% of patients treated with directional atherectomy and in up to 37% of those treated with stenting[5,6]. However, these data derive from randomized studies involving the treatment of more favorable focal, discrete disease. Intracoronary radiation therapy for in-stent restenosis has reduced the rate of recurrent restenosis in native coronary arteries[7-10] and more recently in SVGs[11,12].

We report on a 79-year-old woman with a totally occlusive diffuse in-stent restenosis in a severely degenerated SVG which was successfully reopened and treated with beta brachytherapy.

Case report

A 79-year-old female with a 20-year history of hypertension and hypercholesterolemia was admitted to our Institution in November 2001 with a non-ST-elevation myocardial infarction. Thirteen years previously she had had an anterior non-Q wave myocardial infarction; following the comparison of a three-vessel coronary artery disease she underwent a coronary artery bypass vein graft intervention [four single vein grafts implanted on the left anterior descending artery (LAD), intermediate artery, obtuse marginal branch of the circumflex artery (OM) and right coronary artery (RCA)]. In 1990, following the reappearance of unstable angina, she was submitted to coronary angiography that showed occlusion of the LAD, circumflex artery and RCA as well as occlusion of the SVGs implanted on the OM and intermediate artery and severe stenosis at the distal anastomoses of the RCA-SVG. For this reason she was submitted to coronary angioplasty. In 1999, she underwent multiple stenting of the diffusely degenerated SVG implanted on the LAD (total stent length from the proximal to the distal part of the

graft 52 mm). In the last 3 years prior to presentation in our Institution she had had two episodes of symptomatic (unstable angina) in-stent restenosis of the LAD-SVG treated with stent-in-stent implantation.

After 24 hours of tirofiban infusion (0.1 μg/kg/min) in our hospital she was submitted to repeat coronary angiography.

Procedure. The patient was transferred to the cardiac catheterization laboratory. A 6F sheath was introduced into the right femoral artery. Coronary angiography revealed: occlusion of the three main coronary vessels, chronic occlusion of the SVGs implanted on the OM and intermediate arteries, proximal thrombotic occlusion of the LAD-SVG (Fig. 1) and patency of the RCA-SVG. Since the clinical picture of the patient was severe and since the angiographic findings were suggestive of a recent LAD-SVG occlusion, a coronary intervention was performed. The guide wire that was placed in the distal LAD easily crossed the SVG proximal occlusion. A soft dilation of the proximal part of the graft (CrossSail Guidant, Diegem, Belgium, 3.0-20 mm, 5 atm) was performed but because of the presence of diffuse thrombosis, the whole length of the body graft had to be dilated (CrossSail Guidant 3.0-35 mm, 10 atm) (Fig. 2). Following several dilations and with no protection against the formation of mechanical emboli, the vein graft was reperfused and a TIMI flow 3 was established. The operative outcome of the angioplasty procedure was quite satisfactory with non-significant stenosis in the proximal part of the graft and images indicative of wall thrombosis (quantitative coronary angiography: reference lumen diameter 2.9 mm, minimal lumen diameter 2.3 mm, graft stenosis 21%).

Considering the repeated episodes of in-stent restenosis we decided to submit the patient to radiation therapy (Fig. 3). A 7F sheath was introduced into the right femoral artery and a 7F JR4 (Medtronic, Minneapolis, MN, USA) was used for selective cannulation of the ostium of the LAD-SVG. The procedure was performed using the Galileo system (Guidant), a beta irradiation system (^{32}P), and to avoid the geographic miss phenomenon, we decided to irradiate the body graft totally at a dose of 20 Gy. A multilumen centering balloon catheter (3.0 × 52 mm) that was inflated with normal saline to keep shielding to a minimum was used for this purpose. The dose of radiation to be used was based on the average of the lumen diameters of the proximal and distal reference segments. The distal graft segment was treated first (Fig. 3A). Then the 52 mm balloon was manually retracted (manual tandem positioning) to its proximal part, avoiding a gap of > 4 mm (Fig. 3B). Each segment was treated as a single lesion, and the value of

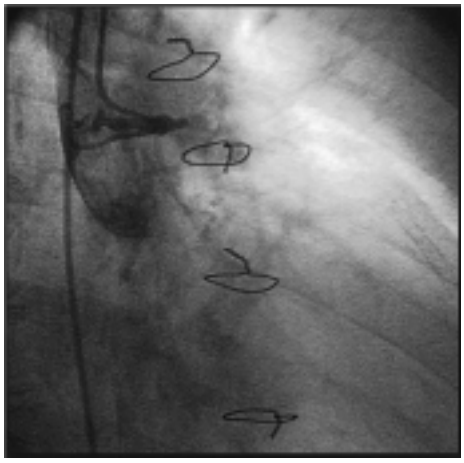

Figure 1. *Angiogram showing subacute occlusion of the saphenous vein graft to the left anterior descending coronary artery.*

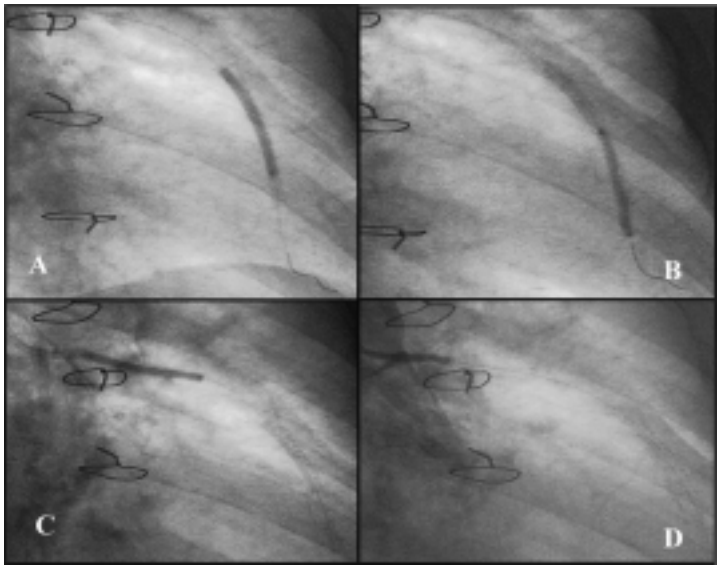

Figure 2. *Mechanical reperfusion of the totally occluded saphenous vein graft. The body graft was dilated from the distal to the proximal anastomosis using a balloon (*A *to* D*).*

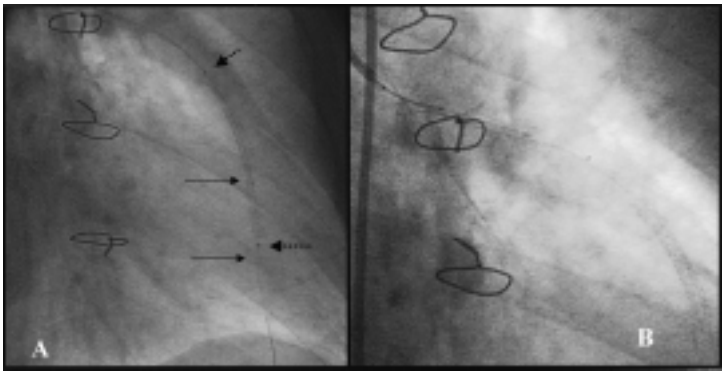

Figure 3. *Brachytherapy procedure.* A: *the Galileo centering catheter (3.0 × 52 mm, between the two* dotted arrows*) was positioned in the mid-distal segments of the saphenous vein graft. The source (20 mm in length and between the two* solid arrows*) initially radiates the most distal of the three-dwell positions and subsequently it is automatically retracted to radiate the other two-dwell positions (automatic stepping procedure).* B: *the Galileo centering catheter (3.0 × 52 mm) was manually retracted (manual tandem positioning) in the mid-proximal segments of the graft to repeat the radiation procedure (automatic stepping procedure).*

the reference lumen diameter was entered with each treatment. Computer controlled advancement and withdrawal of the source wire within the centering balloon was achieved using a high-dose rate after loader. The delivery system calculated the treatment time automatically (426 s in each segment) and performed automated pullback of the 20 mm length source (stepping procedure) inside the centering balloon. The final outcome of the brachytherapy procedure remained satisfactory, with no changes in the distal flow (Fig. 4A). The guiding catheter was removed and tirofiban was maintained for a further 24 hours. No procedural complications occurred and 3 days later the patient was discharged from the hospital and placed on aspirin and ticlopidine (250 mg twice daily) for 12 months.

At a 7-month follow-up visit the patient was asymptomatic, and coronary angiography control revealed no evidence of vein graft restenosis (quantitative coronary angiography: reference lumen diameter 2.8 mm, minimal lumen diameter 1.7 mm, graft stenosis 39%), perforation or aneurysm formation (Fig. 4B).

Discussion

Obstructive lesions in SVGs are a common long-term complication of coronary artery bypass surgery. Redo CABG results in increased perioperative morbidity (3-11%) and mortality (3-7%)[1]. The percutaneous treatment of SVGs is associated with high rates of procedural complications and restenosis particularly in old and diffusely degenerated grafts. Angiographic restenosis at 6 months has been reported in up to 45% of patients treated with directional atherectomy and in up to 37% of those treated with stenting[4,5].

However, these data derive from randomized studies involving the treatment of more favorable focal, discrete disease. No optimal treatment strategy has been clearly defined for patients with diffusely degenerated SVGs, since most of these patients were excluded from clinical trials. Two retrospective studies which included this difficult subset of patients demonstrated that stenting of degenerated SVGs may be successfully performed with acceptable periprocedural complication

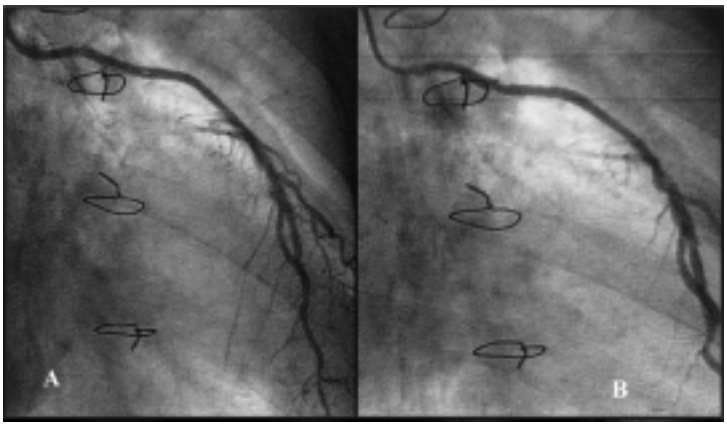

Figure 4. A: *angiogram showing the final procedural result. The angiographic result was satisfactory with non-significant stenosis (residual endovascular thrombosis was still present).* B: *at 7 months of follow-up, the angiographic result was still satisfactory without any significant restenosis.*

rates. However, the long-term event-free survival was disappointing both because of the need for repeat target lesion revascularization and because of the progression of the atherosclerotic disease process[13,14]. In particular, as reported by Choussat et al.[13], at 3 years of follow-up only 17% of the patients were still event-free (death, myocardial infarction and coronary revascularization). Intracoronary radiation therapy for in-stent restenosis in native coronary arteries, using gamma or beta emitters, has reduced the long-term recurrent restenosis rates and brachytherapy is currently considered to be the standard treatment of diffuse in-stent restenosis[7-10].

Recently, Waksman et al.[11] reported the use of a gamma emitting device to address a particularly difficult problem: the treatment of in-stent restenosis within SVGs. In this double-blind study, 120 patients with in-stent restenosis in SVGs and angina pectoris were randomly assigned, after conventional treatment of the restenosis (50% additional stenting), to undergo treatment with ^{192}Ir seeds contained in a ribbon that was positioned within the stent or else with placebo. The mean lesion length in the ^{192}Ir group was 17.6 ± 10.2 mm. No significant in-hospital complications were observed in the treatment group. At 6 months the incidence of in-stent restenosis in the radiation group was reduced by 50% as compared to the placebo group (21 vs 44%, $p < 0.001$). At 12 months, the rate of revascularization of the target lesion was 70% lower in the ^{192}Ir group than in the placebo group (17 vs 57%, $p < 0.001$), and the rate of major cardiac events was 49% lower (32 vs 63%, $p < 0.001$). There was no difference in terms of fatal outcome or myocardial infarction between the two groups. The absolute rates of late thrombosis (2 vs 8%) and total occlusion (2 vs 5%) were lower in the ^{192}Ir group than in the placebo group, despite the use of additional stenting during the intervention in 50% of the patients. More recently Ajani et al.[12], in a study comparing patients with SVG and native coronary artery in-stent restenosis treated with gamma radiation, showed a similar high 6-month event-free survival in both groups (SVG 82% vs native coronary arteries 84%, $p = 0.35$). Data regarding the safety and efficacy of beta irradiation in the treatment of in-stent restenosis in SVG are not yet available. Beta sources are more widely used in European centers because, in comparison with gamma sources, they have a shorter dwell-time, do not need cath-lab shielding, and do not require that the laboratory personnel leaves the room during the treatment. However, due to their physical characteristics, beta particles can travel only finite distances within biological tissues and consequently do not provide the deep tissue penetration that is necessary for the treatment of large vessel lesions. The Galileo system (^{32}P beta radiation system) received Food and Drug Administration approval for the treatment of in-stent restenosis located in vessels with a reference diameter of 3.7 mm.

Our case was really an extreme clinical situation: subacute extensive thrombosis of a SVG probably caused by in-stent restenosis in a diffusely diseased old vein graft. Conventional balloon treatment in conjunction with glycoprotein IIb/IIIa inhibitor upstream administration allowed graft reperfusion with a TIMI flow 3 and a satisfactory angiographic result. Even in this unusual thrombotic context, radiation therapy associated with glycoprotein IIb/IIIa inhibitor administration and prolonged antiplatelet therapy was found to be a safe treatment at the short- and long-term follow-up. Furthermore, in our patient, ^{32}P brachytherapy proved to be highly efficacious in preventing long-term restenosis in an occlusive in-stent restenosis of an old degenerated SVG, irradiated in a very long segment (104 mm). As reported by Nikolsky et al.[15], a total occlusion at baseline represents an independent predictor of major adverse cardiac events during the long-term follow-up in patients with native vessel in-stent restenosis treated with gamma brachytherapy. As shown in Long WRIST, long lesions are more challenging lesions too, requiring higher dose prescriptions to neutralize the increased probability of restenosis[16]. In consideration of all this, the present case highlights the high radiosensitivity of SVG. Our experience is in keeping with Castagna et al.[17] who showed that SVG lesions are more radiosensitive to gamma radiation than native vessel lesions.

In conclusion, this case shows that ^{32}P beta brachytherapy may be highly effective not only in case of native vessel in-stent restenosis but also in high-risk SVG in-stent restenosis. Furthermore, the administration of glycoprotein IIb/IIIa inhibitors and prolonged antiplatelet therapy may render brachytherapy a safe procedure even in the context of extensive thrombosis.

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